Atropisomerism

Metal-mediated transformations to set biaryl chirality

Nathaniel Kadunce
Literature Meeting
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Atropisomerism

- *Atropos*- the “inflexible” or “without turn”
- Arise from hindered rotation about a single bond allowing for isolation of separate conformers

6,6'-dinitro-2,2'-diphenic acid,
the first experimentally described atropisomeric compound

Journal of the Chemical Society, Transactions 121: 614
First Evidence

- Kaufler Hypothesis: *cis* and *trans* isomers explain optical properties
- Supported by a series of misassignments in derivative studies

“...It has been suggested by Carothers and by Mascarrelli that an objection to the Kaufler formula which has never been emphasized is the necessity of bending a bond to an angle of 90°. With a Kekule nucleus such a formula cannot be constructed, and each time that chemists adopt assumptions that cannot be reconciled with the Kekule nucleus they encounter difficulties.” –Adams, 1933

First Evidence

- Kaufler Hypothesis: *cis* and *trans* isomers explain optical properties
- Supported by a series of misassignments in derivative studies
- “It has been suggested by Carothers and by Mascarrelli that an objection to the Kaufler formula which has never been emphasized is the necessity of bending a bond to an angle of 90°. With a Kekule nucleus such a formula cannot be constructed, and each time that chemists adopt assumptions that cannot be reconciled with the Kekule nucleus they encounter difficulties.” –Adams, 1933

Restricted Rotation

1926- The theory of restricted rotation (Turner, Le Fevre, Bell, and Kenyon)

- “Essentially, the theory states that substituents in 2, 2′, 6, 6′ positions in a diphenyl molecule can, by their interference, restrict the free rotation of the two nuclei around the common axis, thus preventing the rings from becoming coplanar and thereby producing in the molecule an asymmetric configuration.” – Adams, 1933

- Proven by resolution with alkaloids and subsequent racemization upon heating, studied extensively by dynamic NMR

Restricted Rotation

- Extensive dynamic NMR studies by Sternhell show direct correlation between van der Waals radii of substituents and energetic barrier to rotation.

- Increasing number of ortho-substituents and van der Waals radius of each decreases the rate of racemization.

- Arbitrary definition of atropisomer is a half life of 1000 seconds at room temperature.

Figure 3. Plot of $\Delta G^\ddagger_{340}$ against the van der Waals radius of X in some 6-(2-X-phenyl)-1,1,5-trimethylindans (I, Y = Me).

In Nature

(+)‐orlandin
anti-plant growth

(−)‐phleichrome
photodynamic ROS generation

ancistrocladine
anti-malarial

biphenomycin A
antibiotic

michellamine A
anti-HIV1 and HIV2
“A potent inhibitor of the antiapoptotic B-cell lymphoma/leukemia-2 (Bcl-2) family of proteins such as Bcl-XL and that the (M)-isomer is some tenfold more cytotoxic than the (P)-isomer.”
Eudysmic Ratios

Derivatization led to increase in activity and in eudysmic ratio from 10 to 24.

Atropchiral Ligands and Catalysts

(R)-BINOL

(R)-DTBM-SEGPHOS

Zhang's D2-symmetric phosphoramidite

(R)-TRIP

(R)-QUINAP

(R,S)-BINAPHOS
Methods and Approaches

Intramolecular Coupling

Chiral tether strategy

Chiral auxilliary strategy

Cr(CO)₃

Intemolecular Coupling

Asymmetric cross-coupling

Asymmetric oxidative cross-coupling

Axial Desymmetrization

"The lactone concept"

Chiral leaving groups

R

R

M

R

R

R'

i-Pr

O

Aux+
Methods and Approaches

**Chiral tether strategy**

**Chiral auxiliary strategy**

**Asymmetric cross-coupling**

**Asymmetric oxidative cross-coupling**

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**Asymmetric cross-coupling**

**Asymmetric oxidative cross-coupling**

**Intermolecular Coupling**

**Axial Desymmetrization**

"The lactone concept"
Redox-Neutral Couplings

1. Enantioposition-selective cross-coupling of a difunctionalized achiral biaryl substrate

2. Dynamic kinetic asymmetric transformations via cross-coupling of a racemic substrate

3. $sp^2$-$sp^2$ Cross-coupling producing axial chirality in the bond-forming event
Enantioposition-selective

a) Kumada-Corriu cross-coupling of aryl Grignard reagent

\[
\begin{align*}
\text{PhMgBr (2 equiv)} & \quad \text{LiBr (1 equiv)} \\
& \quad \text{Et}_2\text{O/PhMe, } -20 \, ^\circ\text{C, 48 h}} \\
\text{(84\% yield, 90\% ee)}
\end{align*}
\]

b) Kumada-Corriu cross-coupling of alkynyl Grignard reagent

\[
\begin{align*}
\text{Ph}_3\text{Si} & \equiv \text{MgBr (2.1 equiv)} \\
& \quad \text{LiBr (1 equiv)} \\
& \quad \text{Et}_2\text{O/PhMe, } 20 \, ^\circ\text{C, 6 h}} \\
\text{(88\% yield, 92\% ee)}
\end{align*}
\]

c) Sonogashira cross-coupling of alkynes

\[
\begin{align*}
\text{[PdCl(\pi-\text{allyl})]_2 (10 mol \%)} & \quad \text{LX (12 mol \%)} \\
& \quad \text{Cul (10 mol \%)} \\
& \quad \text{Et}_3\text{N (2.5 equiv)} \\
& \quad \text{MeCN, } 80 \, ^\circ\text{C, 24 h}} \\
\text{(52\% yield, 63\% ee)}
\end{align*}
\]

Enantioposition-selective

a) Kumada-Corriu cross-coupling of aryl Grignard reagent

\[
\begin{array}{c}
\text{TfO} \quad \text{OTf} \\
\text{PhMe} \\
\end{array}
\xrightarrow{\text{PhMgBr (2 equiv)}} 
\begin{array}{c}
\text{TfO} \quad \text{OTf} \\
\text{Ph} \\
\end{array}
\]

\( \text{LiBr (1 equiv)} \)

\( \text{Et}_2\text{O/PhMe, -20 °C, 48 h} \)

(84% yield, 90% ee)

b) Kumada-Corriu cross-coupling of alkynyl Grignard reagent

\[
\begin{array}{c}
\text{TfO} \quad \text{OTf} \\
\text{Ph} \\
\end{array}
\xrightarrow{\text{Ph}_3\text{Si-MgBr (2.1 equiv)}} 
\begin{array}{c}
\text{TfO} \quad \text{OTf} \\
\text{Ph} \\
\end{array}
\]

\( \text{LiBr (1 equiv)} \)

\( \text{Et}_2\text{O/PhMe, 20 °C, 6 h} \)

(88% yield, 92% ee)

c) Sonogashira cross-coupling of alkynes

\[
\begin{array}{c}
\text{Br} \quad \text{Br} \\
\end{array}
\xrightarrow{\text{[PdCl(\π-allyl)]_2 (10 mol %)}} 
\begin{array}{c}
\text{Br} \quad \text{Br} \\
\end{array}
\]

\( \text{LX (12 mol %)} \)

\( \text{Cul (10 mol %)} \)

\( \text{Et}_3\text{N (2.5 equiv)} \)

\( \text{MeCN, 80 °C, 24 h} \)

(52% yield, 63% ee)

\[ k_{(R)}/k_{(S)} = 5 \]

\[ k_{(R)}/k_{(S)} = 12 \] (85% ee)

major product

Hayashi, 2002 and 2004:

Hayashi, 2002 and 2004:

\[
\text{Ni(cod)}_2 (3 \text{ mol }\%)
\]
\[
i-\text{PrPHOX} (5 \text{ mol }\%)
\]
\[
\text{PhMgX (10 equiv)}
\]
\[
\text{THF, } 20^\circ \text{C, 24 h}
\]

(92% yield, 95% ee)


Lassaletta, 2013:

```
Pd\(_2\)(dba)\(_3\) (5 mol %)
TADDOL–PNMe\(_2\) (5 mol %)
CsCO\(_3\) (2 equiv)
(ArBO)\(_3\) (1.5 equiv)
dioxane, 40 °C, 48 h
(87% yield, 90% ee)
```

Ar = p-MeOPh

DYKAT

Cross-Coupling

-The 1980’s: Asymmetric Kumada-Corriu coupling

\[
\begin{align*}
\text{XX} + \text{XX} & \xrightarrow{[\text{Ni}]/\text{LX}} \text{XX} \\
\text{BPPFA (LX)} & \quad \text{5\% ee} \\
\text{NAPHOS (LX)} & \quad \text{13\% ee} \\
\text{BIPHEMP (LX) w/ Pd} & \quad \text{45\% ee} \\
\text{LX} & \quad \text{40\% yield, 50\% ee} \\
\text{LX} & \quad \text{69\% yield, 95\% ee}
\end{align*}
\]

Ito, Y. et. al. J. Am. Chem. Soc. 1988, 110, 8153
Cross-Coupling

-Skipping ahead to 1999.
Vancomycin

-Skipping ahead to 1999.

- Isolated in 1953 by Eli Lilly from soil bacterium *Amycolatopsis orientalis*.

- Antibiotic used for infections by Gram-(+) bacteria, especially those resistant to more common drugs (e.g. MRSA).

- Inhibits biosynthesis of Gram-(+) bacterial cell wall.
Vancomycin

- No intrinsic substrate control in Suzuki reaction.
- Chiral ligand and condition screening identified BINAP as providing almost complete catalyst control.
- First catalyst-controlled enantioselective Suzuki coupling!

Suzuki Coupling

-The 2000’s, the reign of Boron

Cammidge, 2000:

\[
\text{O} \quad \text{O}
\]

(1.1 equiv)

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{I} & \quad \text{I}
\end{align*}
\]

\[
\begin{align*}
PdCl_2 & (3 \text{ mol } \%) \\
\text{PPFA} & (6 \text{ mol } \%) \\
\text{CsF} & (2 \text{ equiv})
\end{align*}
\]

DME, reflux

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{R} &
\end{align*}
\]

60% yield 85% ee

Buchwald, 2000:

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{P(OEt)}_2 & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{B(OH)}_2 & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
Pd_2(dbac) & (0.2-10.0 \text{ mol } \%) \\
\text{KenPhos} & (2 \text{ equiv}) \\
\text{K}_3\text{PO}_4 & (2 \text{ equiv})
\end{align*}
\]

PhMe, 40-80 °C

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{P(O)(OEt)}_2 &
\end{align*}
\]

98% yield 87% ee

Cammidge, A. N.; Crépy, K. V. L. Chemical Communications 2000, 1723.

Suzuki Coupling

\[
\text{B(OH)}_2 + \text{XX} + \text{XX} \rightarrow \text{Pd/LX} \rightarrow \text{XX}
\]

\( R^1, R^2 = \text{Me, H} \)

\( X = \text{I, Br, Cl} \)

- 65% yield, 54% ee
  (Johannsen, 2003)

- 88% yield, 42% ee
  (Labande, 2010)

- 61% yield, 49% ee
  (Iwasa, 2007)

- 85% yield, 80% ee
  (Kündig, 2014)

- 54% yield, 46% ee
  (Guiry, 2007)

- 95% yield, 94% ee
  (Uozumi, 2009)

- 73% yield, 62% ee
  (Putala, 2013)

- 78% yield, 90% ee
  (Lin, 2010)


Suzuki Coupling

$$\text{B(OH)}_2 + \text{R}_1 \text{X} \text{R}_2 \xrightarrow{\text{Pd/LX}} \text{R}_1 \text{R}_2$$

$R_1, R_2 = \text{alkoxy, H}$

$X = \text{I, Br, Cl}$

---

CyBINAP
92% yield
70% ee
(Mikami, 2004)

BINAP
96% yield
69% ee
(Sawai, 2008)

61% yield
90% ee
(Lassaletta, 2008)

26% ee
(Xiao, 2009)

75% yield
40% ee
(Prim, 2011)

35% ee
(Claver, 2013)

91% yield
60% ee
(Dorta, 2013)

60% yield
55% ee
(Iuliano, 2011)

73% yield
61% ee
(Zhang, 2012)

90% yield
80% ee
(Lassaletta, 2012)

71% yield
50% ee
(Gong/Song, 2014)

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Dorta, R. et al. Synlett 2013, 24, 1215.
Michellamine B

- Isolated in 1991 by Boyd and coworkers
- Anti- HIV-1 (EC$_{50}$ 10 µM) and HIV-2 (EC$_{50}$ 2 µM) activity including resistant strains as well.
- Configurationally labile at binaphthyl junction.
- Significant activity dependence on stereochemistry of naphthylisoquinoline axes.
- Previous approaches: diastereoselective biary coupling; chiral Cr-complexes, and asymmetric lactone cleavage.

Michellamine B

Tang, 2014:

\[
\text{BOPO} + \text{B(OH)}_2 \rightarrow \text{Pd(OAc)}_2 \text{ (1 mol %) Ligand (1.2 mol %) K}_3\text{PO}_4 \text{ (3.0 equiv) PhMe/H}_2\text{O, 35 °C, 12 h} (96\% \text{ yield, 93\% ee})
\]

Tang, 2014:

Building from Buchwald’s work, screened a variety of ligands against various ortho-directing groups, arrived at BOP:

- First catalytic asymmetric preparation of Michellamine B in 20+ years of efforts.
- Very mild conditions employed for hindered Suzuki coupling.

Cross-Coupling: Other Nucleophiles

Zinc: Espinet, 2006

\[
\text{Zn} \quad \begin{array}{c}
\text{Me} \\
\text{Me}
\end{array} + \quad \begin{array}{c}
\text{Me} \\
\text{Br}
\end{array} \quad \xrightarrow{\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 (5 \text{ mol } \%), \text{PPFA} (20 \text{ mol } %)} \quad \begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\]

(1.5 equiv)

THF, 60 °C, 24 h
(95% yield, 85% ee)


Indium: Sarandeses, 2013

\[
\text{In} \quad \begin{array}{c}
\text{Me}
\end{array} + \quad \begin{array}{c}
\text{Me} \\
\text{Br}
\end{array} \quad \xrightarrow{\text{Pd}_2(\text{dba})_3 (2 \text{ mol } %), \text{PPFA} (8 \text{ mol } %)} \quad \begin{array}{c}
\text{Me}
\end{array}
\]

THF, 80 °C, 12–15 h
(71% yield, 86% ee)

Cross-Coupling: Other Nucleophiles

Silicon: Denmark, 2014

- Coordinating substituents at 2-position decrease ee by competitive coordination with Pd.

- Nucleophile/Electrophile swap gives identical ee. Combined with computational work indicates stereodetermining reductive elimination.

Oxidative Coupling- Intro

1. Catalytic asymmetric dimerization of activated phenols and naphthols

2. Oxidative cross-coupling of electronically differentiated arenes
Oxidative Coupling- Nakajima

Nakajima, 1995

R | yield (%) | ee (%) |
---|---|---|
CO₂Me | 85 | 78 |
CO₂Et | 77 | 73 |
CO₂Bn | 77 | 76 |
CO₂t-Bu | 69 | 58 |
H | 89 | 17 |
i-Pr | 58 | 5 |
OBn | 95 | 24 |

## Oxidative Coupling - Kozlowski

**Kozlowski, 2001**

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^1$</th>
<th>Catalyst Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{CO}_2\text{Me}$</td>
<td>$(S,S)$</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>$\text{CO}_2\text{Me}$</td>
<td>$(R,R)$</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>$\text{CO}_2\text{Bn}$</td>
<td>$(S,S)$</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>$\text{CO}_2n\text{-Hx}$</td>
<td>$(S,S)$</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>$\text{CON(CH}_2\text{CH}_2\text{)}_2\text{O}$</td>
<td>$(S,S)$</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>$\text{COPh}$</td>
<td>$(S,S)$</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>$\text{OBn}$</td>
<td>$(R,R)$-$\text{CuBr}$</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>$\text{P(O)(OMe)}_2$</td>
<td>$(S,S)$</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>$\text{SO}_2\text{C}_6\text{H}_4^+p\text{-OMe}$</td>
<td>$(S,S)$</td>
<td>75</td>
</tr>
</tbody>
</table>

The Perylenequinones

- Commonly isolated fungal natural products. Sources include *Cercospora kikuchii*, cause of soy bean “purple speck disease.”

- Possess helical chirality about the core pentacycle. Atrop-stability varies among members of the family.

- Light-induced biological activity (singlet oxygen generation, ROS) makes them potential photodynamic therapeutics.
Perylenequinone Syntheses

Kozlowski, 2009

Prepared from common intermediate:

Perylenequinone Syntheses

Kozlowski, 2009

Interesting bisquinone closure with MnO$_2$:

Oxidative Couplings

Ha, 2004

Pilati, 2003

Troin, 2011

Pal, 2008

Martell, 2003

Habaue, 2004

Oxidative Coupling - Vanadium

Chen, 2001 (72% yield, 65% ee)
Uang, 2002 (90% yield, 54% ee)
Jiang, 2002 (62% yield, 90% ee)
Chen, 2002 (99% yield, 84% ee)

Gong, 2002 (95% yield, 83% ee)
Sasai, 2008 (76% yield, 91% ee)

Oxidative Coupling - Ruthenium

Katsuki, 2000

Oxidative Heterocoupling

Habaue, 2007

- Selective oxidation of more electron-rich naphthol
- Cross-selectivity achieved by activating chelating substrate with Lewis acid
- No mechanistic details reported

Oxidative Heterocoupling

Itami, 2012

\[
\begin{align*}
\text{Me} & \\
\text{Me} & \\
\text{S} & \\
\text{Me} & \\
\text{Me} & \\
\text{+} & \\
\text{Pr} & \\
\text{B(OH)}_2 & \\
(4 \text{ equiv}) & \\
+ & \\
\text{Me} & \\
\text{Me} & \\
\text{S} & \\
\text{Pr} & \\
\text{B(OH)}_2 & \\
\text{sox} & \\
\text{ligand} & \\
\end{align*}
\]

Pd(OAc)_2 (10 mol %)

\[
i-\text{PrBIOX} \ (10 \text{ mol } %)
\]

TEMPO (4 equiv)

\[
^\text{iPrOH}, \text{70 °C, 12 h}
\]

(27% yield, 72% ee)

or

Pd(OAc)_2 (sox) (10 mol %)

\[
\text{FePc} \ (5 \text{ mol } %)
\]

DMA, 70 °C, 24 h

(61% yield, 61% ee)


Conclusion

- Metal-catalyzed asymmetric biaryl cross-coupling has developed into a rich and synthetically useful field.

- Both redox-neutral and oxidative methods have been optimized and employed in complex settings.

- Oxidative cross-coupling and non-Mg, non-B redox neutral cross-coupling are underdeveloped emerging fields with significant potential.
Resources

• Kevin Allen's group meeting, 2005:
  – Excellent coverage of diastereoselective methods and chiral leaving groups
    http://stoltz.caltech.edu/seminars/2005_Allan.pdf

• B. Collins (Denmark) group meeting, 2004:
  – Detailed descriptions of Vanadium oxidative reactions and aryl-Pb couplings

• M. Bruening review, 2011
  – Atroposelective Total Synthesis of Axially Chiral Biaryl Natural Products

• M. C. Kozlowski review, 2013
  – Aerobic Copper-Catalyzed Organic Reactions
    Chem. Rev., 2013, 113 (8), pp 6234-6458